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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,087	10/02/2001	Sobha M. Pisharody	302-000110US	9522

7590 11/17/2003

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,087	PISHARODY ET AL.	
	Examin r	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on th cov r she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-15,20-39 and 41-207* is/are pending in the application.

4a) Of the above claim(s) *41-165* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-15,20-39 and 166-207* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in the paper filed August 20, 2003 is acknowledged.

Claim Interpretation

2. The claims are drawn to a molecular sensing apparatus with electrode pairs where a portion of the insulator is "removed" to form a channel and where the electrodes are separated by a distance that permits a biological macromolecule to connect the electrode pairs. First, since this is a product claim, there is no structural distinction between a product where the insulator was removed and a product where the insulator originally contained a channel or where, in fact, no insulator was originally present, since the entire removal of the insulator would be equivalent structurally to absence of the insulator. Second, claims 1-33, for example, have no requirement that a biological macromolecule be attached and therefore simply read on any device that has two electrodes and an insulator with something that can be deemed a channel. Third, with regard to the distance that can be spanned by a biological macromolecule, Official Notice is taken that an average chromosome may be 5 centimeters (equivalent to 5 x 10^4 micrometers) in length when stretched out (see http://hypertextbook.com/facts/1998/StevenChen.shtml, for example).

Claim Rejections - 35 USC § 112 – Second Paragraph

3. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by "said as least" in claim 25. It is unclear if the "as" should be "at" or if some phrase after the term "said" was inadvertently deleted.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1, 5-7, 11, 20-24, 166, 167, 171, 173, 174, 183, 192, 205 and 206 are rejected under 35 U.S.C. 102(b) as being anticipated by Ueda et al (Japanese J. Appl. Phys. Pt. 1 (1999) 38(4A):2118-2119.

Ueda teaches an apparatus of claims 1 and 166 comprising:

An electrode pair (see figure 1, panel b) comprising

A first electrode (see figure 1, panel b),

A second electrode (see figure 1, panel b),

Which pair is formed on a glass plate which is an insulator (see page 2118, column 1) with a microgap of 80 micrometers (see page 2118, column 1),

Wherein said first and second electrode are separated by a distance that would allow a biological macromolecule to connect the first electrode to the second electrode (see page 2118, column 1, where the gap is 80 micrometers, which is a distance significantly less than the 5 centimeters of a chromosome).

With regard to claims 5, 173, the glass plate of Ueda inherently has a resistivity of greater than 10^{-3} ohm-meters (see, for evidence, http://www.burle.com/cgi-bin/byteserver.pl/pdf/tp183.pdf).

With regard to claim 6, the glass plate of Ueda is composed of SiO_2.

With regard to claim 7, 167, 171, Ueda teaches a microgap of 80 micrometers which would permit a chromosome or even a YAC to overlap (see page 2118, column 1, which is less than 10^{10} angstroms (which is a 1 meter separation).

With regard to claims 11, 174, Ueda teaches aluminum electrodes (see figure 1).

With regard to claims 20-24, 183, 206, Ueda teaches an apparatus where the first and second electrodes are integrated with the glass insulator to form a substrate with a uniformly patterned surface that is planar (see figure 1 and page 2118, column 2) but Ueda also teaches that the electrode formed a slope in the vacuum evaporation method so that the two electrodes are not coplanar (see page 2118, column 2) unlike in the photolithography method (see page 2118, column 2).

With regard to claims 192, 205, Ueda shows biological molecules attached to both electrodes (see figure 1).

6. Claims 1, 5-7, 9-13, 20-31, 34-39, 166-171, 173-176, 179, 181, 183-189, 191-201, 203 and 205-207 are rejected under 35 U.S.C. 102 (b) and (e) as being anticipated by Eichen et al (US 2003/0203394 A1, effective filing date in US of March 1, 2001) and Eichen (WO 99/57550). (for ease of explanation, the U.S. patent will be used for the identification).

Eichen teaches an apparatus of claims 1 and 166 comprising:

An electrode pair (see figure 7, panel a) comprising

A first electrode (see figure 7, panel a),

A second electrode (see figure 7, panel a),

Which pair is formed on a glass plate which is an insulator (see page 12, paragraph 0192) with a microgap of 12 micrometers (see page 13, paragraph 0127 and page 7, paragraph 0112),

Wherein said first and second electrode are separated by a distance that would allow a biological macromolecule to connect the first electrode to the second electrode (see page 13, paragraph 0127 and page 7, paragraph 0112, which distance is less than the lambda DNA used to bridge the gap).

With regard to claims 5, 173, the glass plate of Eichen inherently has a resistivity of greater than 10^{-3} ohm-meters (see, for evidence, http://www.burle.com/cgi-bin/byteserver.pl/pdf/tp183.pdf).

With regard to claim 6, the glass plate of Eichen is composed of SiO_2.

With regard to claim 7, 167, 171, Eichen teaches a microgap of 12 micrometers which would permit lambda DNA to overlap (see page 13, paragraph 0127 and

page 7, paragraph 0112, which is less than 10^{10} angstroms (which is a 1 meter separation).

With regard to claims 9, 10, 173, Eichen demonstrates low resistance electrodes with a calculated resistance at some points in the graph of less than 10^{-2} ohm meters (see figures 19 and 20 and paragraph 0115).

With regard to claims 11, 174, Eichen teaches formation of gold based electrodes (See paragraph 0187, 0217).

With regard to claims 12, 13, 175, 176, 179, 181, 200-201, 203, Eichen teaches chemical derivatization of the electrode with a disulfide group (see paragraph 0217) as well as thiol linkers, biotin streptavidin or other linker types (see page 11).

With regard to claims 20-24, 183, 206, Eichen teaches an apparatus where the first and second electrodes are integrated with the glass insulator to form a substrate with a uniformly patterned surface that is planar (see figure 7, panel a and page 19, example 27,) but Eichen also teaches that the electrode formed in two different plantes (see page 19, example 29).

With regard to claims 25-28, 184-186, Eichen teaches detection of up to 1,000,000 different sites, each representing an electrode pairs, yielding 10^6 electrode pairs (see page 19, example 27).

With regard to claim 29, 31, 187, 189, Eichen teaches connecting a measurement device that is electrically coupled to the electrodes (see page 19, example 27, for example, also see page 15, example 12) to form an electric circuit (see examples 12, 26 and 27).

With regard to claim 30, 188, Eichen shows measurement of current and voltage (see figure 19, for example).

With regard to claims 34-35, 191, 205, Eichen teaches attachment of different biological macromolecules to the electrodes including biological molecules which connect the two electrodes (see paragraph 0298 and figure 7, panel a for example).

With regard to claim 36, 193, Eichen teaches computer control (see paragraph 0299).

With regard to claims 37-39, 194-196, Eichen teaches semiconductors (see paragraph 0155 and 0211, for example, including silicon, see paragraph 0300).

With regard to claims 168-170, 197-199, 207, Eichen teaches connection of the electrodes by DNA (see example 8).

With regard to claims 192, 205, Eichen shows different biological molecules attached to both electrodes (see figure 7 and example 27, page 19).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 8 and 172 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eichen (WO 99/57550) as applied to claims 1, 5-7, 9-13, 20-31, 34-39, 166-171, 173-176, 179, 181, 183-189, 191-201, 203 and 205-207 above.

Eichen teaches an apparatus of claims 1 and 166 comprising:

An electrode pair (see figure 7, panel a) comprising

A first electrode (see figure 7, panel a),

A second electrode (see figure 7, panel a),

Which pair is formed on a glass plate which is an insulator (see page 12, paragraph 0192) with a microgap of 12 micrometers (see page 13, paragraph 0127 and page 7, paragraph 0112),

Wherein said first and second electrode are separated by a distance that would allow a biological macromolecule to connect the first electrode to the second electrode (see page 13, paragraph 0127 and page 7, paragraph 0112, which distance is less than the lambda DNA used to bridge the gap).

With regard to claims 5, 173, the glass plate of Eichen inherently has a resistivity of greater than 10^{-3} ohm-meters (see, for evidence, http://www.burle.com/cgi-bin/byteserver.pl/pdf/tp183.pdf).

With regard to claim 6, the glass plate of Eichen is composed of SiO_2.

With regard to claim 7, 167, 171, Eichen teaches a microgap of 12 micrometers which would permit lambda DNA to overlap (see page 13, paragraph 0127 and page 7, paragraph 0112, which is less than 10^{10} angstroms (which is a 1 meter separation).

With regard to claims 9, 10, 173, Eichen demonstrates low resistance electrodes with a calculated resistance at some points in the graph of less than 10^{-2} ohm meters (see figures 19 and 20 and paragraph 0115).

With regard to claims 11, 174, Eichen teaches formation of gold based electrodes (See paragraph 0187, 0217).

With regard to claims 12, 13, 175, 176, 179, 181, 200-201, 203, Eichen teaches chemical derivatization of the electrode with a disulfide group (see paragraph 0217) as well as thiol linkers, biotin streptavidin or other linker types (see page 11).

With regard to claims 20-24, 183, 206, Eichen teaches an apparatus where the first and second electrodes are integrated with the glass insulator to form a substrate with a uniformly patterned surface that is planar (see figure 7, panel a and page 19, example 27,) but Eichen also teaches that the electrode formed in two different plantes (see page 19, example 29).

With regard to claims 25-28, 184-186, Eichen teaches detection of up to 1,000,000 different sites, each representing an electrode pairs, yielding 10^6 electrode pairs (see page 19, example 27).

With regard to claim 29, 31, 187, 189, Eichen teaches connecting a measurement device that is electrically coupled to the electrodes (see page 19,

example 27, for example, also see page 15, example 12) to form an electric circuit (see examples 12, 26 and 27).

With regard to claim 30, 188, Eichen shows measurement of current and voltage (see figure 19, for example).

With regard to claims 34-35, 191, 205, Eichen teaches attachment of different biological macromolecules to the electrodes including biological molecules which connect the two electrodes (see paragraph 0298 and figure 7, panel a for example).

With regard to claim 36, 193, Eichen teaches computer control (see paragraph 0299).

With regard to claims 37-39, 194-196, Eichen teaches semiconductors (see paragraph 0155 and 0211, for example, including silicon, see paragraph 0300).

With regard to claims 168-170, 197-199, 207, Eichen teaches connection of the electrodes by DNA (see example 8).

With regard to claims 192, 205, Eichen shows different biological molecules attached to both electrodes (see figure 7 and example 27, page 19).

Eichen et al does not expressly teach separations of less than 70 angstroms.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to optimize the method of Eichen with regard to the separation distance since Eichen states "Electrodes 300 are spaced from one another at a distance which should not exceed the combined length of the target DNA

sequences 310 and the recognition moieties 306 and 308 (see page 10, paragraph 0152)." Thus, Eichen motivates an ordinary practitioner to modify the results optimizable variable of electrode separation to achieve the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific distances for spacing of the electrodes was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

10. Claims 14, 15, 177, 178, 180, 182, 202 and 204 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eichen (WO 99/57550) as applied to claims 1, 5-13, 20-31, 34-39, 166-171, 173-176, 179, 181, 183-189, 191-201, 203 and 205-207 above in view of Eckhardt et al (U.S. Patent 6,127,127).

Eichen teaches and suggests the limitations of claims 1, 5-13, 20-31, 34-39, 166-171, 173-176, 179, 181, 183-189, 191-201, 203 and 205-207 as discussed above.

Eichen does not teach the use of self assembled monolayers on the electrodes.

Eckhardt teaches the use of self assembled monolayers on the electrodes (see column 4, line 58 to column 5, line 40, for example).

With regard to claim 15, Eckhardt teaches alkanethiol attachments (see column 8, line 55 and column 2, line 57, for example).

With regard to claim 180, Eckhardt teaches phosphonates (see column 4, line 58, for example).

With regard to claim 182, Eckhardt teaches NHS linkers (see column 16, example 4).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the electrodes of Eichen with the self assembled monolayers of Eckhardt in order to permit DNA attachment since Eckhardt teaches "Thus, the self-assembled monolayer is non-conductive, serves to immobilize reactants near the electrode surface, and allows the transition metal complex to move freely from the immobilized reactants to the conductive working surface of the electrode to permit electron transfer (see column 5, lines 18-22)." An ordinary practitioner would have been motivated to combine the methods of Eichen and Eckhardt in order to achieve attachment of the nucleic acid to the electrode in a way which permits electron transfer as taught by Eckhardt.

11. Claims 32, 33 and 190 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eichen (WO 99/57550) as applied to claims 1, 5-13, 20-31, 34-39, 166-171, 173-176, 179, 181, 183-189, 191-201, 203 and 205-207 above in view of Kovacs et al (5,965,452).

Eichen teaches and suggests the limitations of claims 1, 5-13, 20-31, 34-39, 166-171, 173-176, 179, 181, 183-189, 191-201, 203 and 205-207 as discussed above.

Eichen does not teach the use of CMOS gates in biosensor applications.

Kovacs teaches the use of CMOS gates for detection of electrical signals in biosensor applications (see column 5, lines 43-52).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the apparatus of Eichen to take advantage of the CMOS gates and detection apparatus of Kovacs since Kovacs states "It is another object of the present invention to provide an improved biologic electrode site which includes a sample and hold circuit and which may be fabricated using conventional CMOS semiconductor fabrication techniques (see column 4, lines 25-45)." An ordinary practitioner would have been motivated to improve the electrode of Eichen for the detection of DNA by using the electrode and circuit system of Kovacs in order to have an improved electrode and the ability to fabricate the system using conventional CMOS techniques.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634